PATENT

A COMPOSITION AND METHOD FOR THE TREATMENT OF ONYCHOMYCOSIS IN ANIMALS

RELATED APPLICATIONS

[0001] This application is a divisional of co-pending application serial number 09/545,486 which claims the priority filing date of the Provisional application serial number 60/128,604, filed April 8, 1999.

FIELD OF THE INVENTION

[0002] This invention relates to a composition and method for the prevention and treatment of fungal infections such as sporotrichosis, onychomycosis infections, hoof rot, jungle rot, pseudallecheria boydii, scopulariopsis, athletes foot, canker sole and fungal infections generally. The composition of the present invention is useful for the treatment of fungal infections in warm-blooded animals such as humans and horses. The method of

the present invention is directed to the application of a therapeutic amount of the present composition.

BACKGROUND OF THE INVENTION

[0003] Conditions such as onychomycosis and other fungal infections pose serious problems in dermatology. It has been estimated that the prevalence of onychomycosis in the general population is in the range of 2-13% and increases to about 15-20% in the 40-60 year old age group. Onychomycosis is a condition recognized by discoloration beneath toe nails and finger nails along with pain when pressure is placed near or at the site of discoloration. The condition usually affects more than one nail. Various fungi, classified as white superficial fungi, cause the condition. Frequently the condition is treated by the combination of nail avulsion and application of a pharmaceutical agent. Presently available topical antifungal formulations for treating fungal infections have been met with limited success. This is primarily due to the limited ability of such compounds to penetrate into the nail plate, which is hyperkeratotic. The treatment of the condition is further problematic in geriatric patients where therapeutic options are often limited due to possible drug interactions, systemic side effects of treatment, and contraindications secondary to other medical ailments.

[0004] The treatment of fungal infections of the nail and hoof generally falls into three categories: systemic administration of antifungals; surgical removal of all or part of the nail or hoof followed by topical treatment of the exposed tissue; or topical application of conventional creams, lotions, gels or solutions, frequently including the use of

bandages to keep these dosage forms in place on the nail or hoof. All of these approaches have major drawbacks.

[0005] Long term systemic (oral) administration of an antifungal agent for the treatment of onychomycosis is often required to produce a therapeutic effect in the nail bed. For example, oral treatment with the antifungal compound ketoconozole typically requires administration of 200 to 400 mg/day for 6 months before any significant therapeutic benefit is realized. Such long term, high dose systemic therapy can have significant adverse effects. For example, ketoconozole has been reported to have liver toxicity effects and reduces testosterone levels in blood due to adverse effects on the testes. Patient compliance is a problem with such long term therapies especially those which involve serious adverse effects. Moreover, this type of long term oral therapy is inconvenient in the treatment of a horse or other ruminants afflicted with fungal infections of the hoof.

[0006] Accordingly, the risks associated with parenteral treatments generate significant disincentive against their use and considerable patient non-complience. However, these and other related hindrances to treatment can be potentially avoided through the appropriate use of a therapeutically effective of a composition according to the present invention. Moreover, the present invention provides a method for the administration of an effective amount of the present invention comprising the application of the composition to an area in need of treatment and maintaining the composition in contact therewith for an effective period of time.

[0007] Surgical removal of all or part of the nail followed by topical treatment also has severe drawbacks. The pain and discomfort associated with the surgery and the undesirable cosmetic appearance of the nail or nail bed represent significant problems, particularly for female patients or those more sensitive to physical appearance. Generally, this type of treatment is not realistic for ruminants such as horses.

[0008] Topical therapy has significant problems too. Topical dosage forms such as creams, lotions, gels etc., can not keep the drug in intimate contact with the infected area for therapeutically effective periods of time. Bandages have been used to hold drug reservoirs in place in an attempt to enhance absorption of the pharmaceutical agent. However the bandages are thick, awkward, troublesome and generally lead to poor patient compliance.

[0009] Hydrophilic and hydrophobic film forming topical antifungal solutions have also been developed. These dosage forms provide improved contact between the drug and the nail, but the films are not occlusive. Topical formulations for fungal infection treatment have largely tried to deliver the drug to the target site (an infected nail bed) by diffusion across or through the nail.

[0010] Nail is more like hair than stratum corneum with respect to chemical composition and permeability. Nitrogen is the major component of the nail attesting the to the nail's proteinaceous nature. The total lipid content of mature nail is 0.1-1.0%, while the stratum corneum lipid is about 10% w/w. The nail is 100-200 times thicker than the stratum corneum and has a very high affinity and capacity for binding and retaining antifungal drugs. Consequently little if any drug penetrates through the nail to

reach the target site. Because of these reasons topical therapy for fungal infections have generally been ineffective.

[0011] Compounds known as penetration or permeation enhancers are well known in the art to produce an increase in the permeability of skin or other body membranes to a pharmacologically active agent. The increased permeability allows an increase in the rate at which the drug permeates through the skin and enters the blood stream. Penetration enhancers have been successful in overcoming the impermeability of pharmaceutical agents through the skin. However, the thin stratum corneum layer of the skin, which is about 10 to 15 cells thick and is formed naturally by cells migrating toward the skin surface from the basal layer, has been easier to penetrate than nails. Moreover, known penetration enhancers have not proven to be useful in facilitating drug migration through the nail tissue.

[0012] Antimicrobial compositions for controlling bacterial and fungal infections comprising a metal chelate of 8-hydroxyquinoline and an alkyl benzene sulfonic acid have been shown to be efficacious due to the increased ability of the oleophilic group to penetrate the lipoid layers of micro-cells. The compounds however, do not effectively increase the ability to carry the pharmaceutically active antifungal through the cornified layer or stratum corneum of the skin. U.S. Pat. No. 4,602,011, West et al., Jul. 22, 1986; U.S. Pat. No. 4,766,113, West et al., Aug. 23, 1988.

[0013] The composition of the present invention is directed a method and composition for treating onychomychosis, and related infections, in animals. Because

onychomychosis is an infection afflicting all animals with a nail or hoof, this composition is useful in the treatment of any animal with a nail or hoof.

[0014] Onychomychosis is a fungal infection of the nail or hoof bed. Because the infection is under the nail or hoof it is very dificult to treat. Traditional methods of treatment involve complete nail removal in humans. Not infrequently the chosen treatment regime involves nail removal combined with topical treatment of the now exposed infected tissue. However, the removal of an infected hoof requires complete imobilization of the animal, an often impossible task. This treatment regime is therefore unreasonable for the treatment of hoofed animals, such as horses.

[0015] Topical treatments have also been employed. However, because the nail is largely impervious to the transfer of drugs, little of the applied drug reaches the infected tissue. This problem is more pronounced in hoofed animals where the nail is many time thicker than the nail of a human.

[0016] However if white line disease is allowed to grow unchecked, it can result in the crippling of the animal.The unbchecked growth of the fungus in humans often inflicts substantial pain.

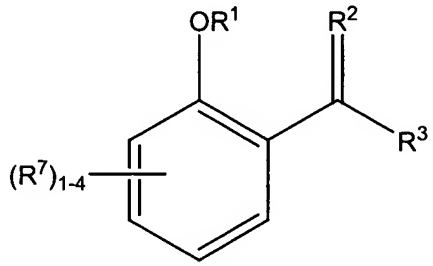
[0017] The inventor has solved the problem of treating a human afflicted with onychomychosis, without surgery. Moreover, the present invention solves this long felt need through the formulation of a composition which has unique properties relative to migration into the infected site.

[0018] It would therefore be useful to provide a composition for the treatment of onychomychosis and related infections in animals.

[0019] It would further be useful to provide a mehtod for the administration of the present composition for the treatment of onychomychosis in animals.

DESCRIPTION OF THE INVENTION

[0020] These and other objects of the invention are accomplished through a method of treatment of the infected nail or hoof and a composition to be applied to the infected nail/hoof comprising a composition consisting essentially of a compound according to firmula I:



(I)

Where R^1 is hydrogen;

R^3 is hydroxy;

R^2 is hetero;

each R^7 is independently hydrogen, alkyl, hetero, heteroalkyl, aryl or heteroaryl and ;

a copper composition;

a peroxide;

a polyhydroxy aromatic compound;

a transition metal coordination complex;

all dissolved in water, wherein the composition contains greater than 100 mg copper composition.

[0021] The composition according to the present invention is directed to the treatment of fungal infections in animals comprising:

[0022] at least one element such as an element selected from columns IIa through column VIa of the periodic chart of the elements, preferably an element selected from columns IIa through column IVa and most preferably a transition metal selected from the group comprising column IIIb to column IIb and where the element is in ionic form. The element in ionic form means an element in a state other than its elemental state, such Cu^{+2} or Cu^{+1} or Ag^{+1}. The element in ionic form can be from any source, but usually from the oxide, carbonate, hydroxide or other salt of the element such as $CuSO_4$, CuO, $CuOH_2$ or Ag_2SO_4.

[0023] at least one chelating or complexing agent selected from the group consisting of a carboxylic acid, hydroxyaryl carboxylic acid, thioaryl carboxylic acid, a heteroaryl carboxylic acid, a heteroatom substituted aryl carboxylic acid, a hydroxy heteroaryl carboxylic acid, crown ether, hetero crown ether, tributyl tin oxide, thiol, diamine, triamine, glycols thioglycols and aminoglycols.

[0024] In the composition according to this invention the metal, the chelating or complexing agent and optionally a peroxide are combined in a polar solvent at a suitable temperature and for a suitable period of time to allow the solvation of the added ingredients.

[0025] Although not wanting to be bound by any theory or presented hypothesis, a brief analysis of the chemistry involved may be useful in understanding the invention.

[0026] It is known that transition metals are cytotoxic if introduced into a cell. For example, I_2 is bactericidal when applied topically, and the use of metallic copper as an antibiotic is also known. It is therefore believed that the introduction of a toxic metal into the cellular system of the fungal organism will cause it to die. The present invention seems to cause, or at least assists in the introduction of a metal into the cellular system of the fungus. This is accomplished through the formation of a chelate, complex or salt between a metal and an organic agent such as salicylic acid or thiosalicylic acid and administering this composition to the infected site. The formation of any one specific chelate or complex structure is not essential for the proper functioning of the composition nevertheless, a complex of undetermined structure is likely formed in solution. In this regard, it is desirable that the amount of the complexing agent be in greater amounts than the metal in the composition, e.g. that the complexing agent and the metal be in a ratio of greater than 1:1, complexing agent:metal.

EXAMPLES

Example 1

[0027] The treatment solution was prepared by adding about 100-300 grams of salicylic acid to 4 Liters of warm water. This was followed by 10-100 g NaOH and 1-60 grams of boric acid. The solution was mixed and filtered to remove traces of undissolved

material. Then about 1-100 grams of copper sulfate where added and the solution became a light green. Finally, the solution was diluted to 20L with water.

Example 2

[0028] To 1 liter of water is added 20 grams of thiosalicylic acid and 0.5 grams copper sulfate. The solution is stirred sufficiently to allow proper mixing. The solution changes from blue to amber, indicating that an association with the copper and the complexing agent has formed.

Example 3

[0029] The treatment solution was prepared by adding about 230 grams of salicylic acid to 4 Liters of warm water. This was followed by 45 g NaOH and 25 grams of boric acid. The solution was mixed and filtered to remove traces of undissolved material. Then 10 grams of copper sulfate where added and the solution became a light green. The solution was allowed to cool and 1-100 mL of hydrogen peroxide was added. Finally, the solution was diluted to 20L with water.

Example 4

[0030] The treatment solution was prepared by adding about 230 grams of salicylic acid to 4 Liters of warm water. This was followed by 45 g NaOH and 25 grams of boric acid. The solution was mixed and filtered to remove traces of undissolved material. Then 50 grams of copper sulfate where added and the solution became a light green. The solution was allowed to cool. Finally, the solution was diluted to 20L with water.

[0031] Salts of any metal may be used but water soluble metal salts are preferred and water soluble salts of Ag, Cu, Ni and Co are most preferred.

[0032] An organic moiety complexing agent such as an aryl carboxylic acid, a hydroxyaryl carboxylic acid and a thioaryl carboxylic acid are preferred and salicylic acid and thiosalicylic acid are most preferred.

[0033] The inclusion of a peroxide, although optional, may be included from the group comprising: organic and inorganic peroxides such as hydrogen peroxide, benzoyl peroxide and acetyl peroxide.

[0034] The above fungal infection treating composition is applied in any manner that places the composition is contact with the infected tissue. One method of application involves the use of a syringe with out the needle. A syringe of suitable size is loaded with the composition and sprayed or squirted in the space between the hoof of the infected animal and the attached tissue. Substantial amounts of black, decayed tissue and rotting matter may be discharged after the first washing. A second application is recommended to ensure the delivery of adequate amounts of the fungal treating composition to the infected tissue.

[0035] The infected area may also be treated through the use of cloth soaked in the fungal treating composition of the present invention. For example, a cloth soaked in the composition may be inserted into the space between the hoof and the attached tissue so that the soaked cloth is in intimate contact with the infected tissue, thereby placing the fungal treating composition in contact with the infected tissue.

[0036] In general the infected tissue may be treated in any method or manner that causes the infected tissue to be contacted with the fungal treating composition of this invention.